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OFFICE OF THE PRESIDENT

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Dear Tom:

Thank you for your letter of October 11th. I will give you a partial answer to those questions that I can respond to promptly and will go on further a little later on.

1 & 2. Authorship of the 1947 papers. My recollections on many of these matters are becoming rather dim but fortunately I have found a scrap of correspondence from Francis Ryan that does illuminate it. In retrospect I have to remark that as a very young student I did not appreciate that my seniors -- especially someone like Ed Tatum -- still had their own need for recognition. But they did, and, for the role that I have described in my memoir, entirely deservedly. The logic of the specific allocation of authorship would have included the following factors:

Ed's historic specialty and reference group was microbiology; so he was the senior author of the J. Bact. paper. He had of course in his previous publications contributed a great deal of conceptual background about nutritional mutants, and how to isolate them, which made J. Bact. all the more appropriate.

Genetics was my own "specialty" and particularly when it came to details of mapping, Ed would have made no claims at all. In addition, as this work was also to serve as my Ph.D. dissertation it would (in those days) have been terribly awkward to present material that was not explicitly of my sole authorship. (There is nothing noteworthy in the dissertation text itself beyond what has appeared in print.) It did create a little bit of a stir and precedent at Yale that it comprised no more than a score or so of typewritten pages plus a number of reprints, the ones you know about. As you know, I did do all of the experiments myself. I believe I did display them to Ed in enough detail that he was able to offer a critical judgement as to their validity; and his general inspirational background you also know as well. I am very sorry I do not have early drafts of the manuscripts to be able to recall exactly what editorial input Ed put into the papers: of course he read them and I am sure he did have some editorial comment.

Through item 3 I had also worked on *Neurospora* with Ryan; and the concepts of relative sexuality coming out of Hartman's work were quite familiar to me. It was not so much

Hayes' work but our own with the early findings on HFR (which came in the first instance from Cavalli) and with F+ and F- strains where that came in. In fact the matter deserves more looking into. I do not think it has been: that is to say the extent to which F+ strains show some diminution of receptivity (I functioning as F-) in crosses with other F+ or HFR. If you have picked up some more work on this theme I'd be interested to be reminded of it. It does come up again in the yeast mating type story, I believe.

Medicine. No I do not think I ever had any intention of clinical practice but I did have in mind research with a possibly strong clinical flavor. If I'd had to make a choice in 1944 I would have identified neurology as the most promising area from that perspective. I did not know as much as I do now about the interrelationship of medical qualifications, medical practice and medical research; and indeed the times have changed in a very fundamental way about the role of non-M.D.'s in medical schools and in medical research.

Your question 5. What did Luria and Delbruck really prove? I am responding to the fairly frequent but loose assertion that their experiment "proved that bacteria have genes". The problem that their experiments actually address is whether mutation occurs spontaneously or is a post-adaptive phenomenon, evoked by the agent used for the selection and enumeration of the variants. The null hypothesis of the fluctuation test is that uniform environments at the time of selection -- if selection is what induces the mutation -- should give you Poisson distributions of the numbers of mutants from cultures to culture. If each cell responds uniformly to the selective/post-mutational stimulus with equal probability then that is a reasonable expectation and the fluctuation found would refute it. However, one can argue that there is no way to prove that the environment from one test tube to another is so uniformly constant that it fulfills the stipulated condition. That is a rather farfetched exception but it does focus attention on what the fluctuation test actually endeavors to prove. (To account for what was actually reported in 1943, one could also have invoked large fluctuations from moment to moment in responsivity to phage within the same culture! Later work with the chemostat showing the secular increase in mutant number is more persuasive.) The preadaptive occurrence of phage resistant mutations had already been remarked upon by several authors, notably F.M. Burnet who had no trouble in fishing out R mutants on the basis of colonial appearance and then showing that they were cultures resistant to S specific phages.

The more important point is the relationship between the problem they were attacking: the spontaneity of mutation versus the many other connotations of the assertion that "bacteria have genes". There is quite a good discussion of bacterial variation in Dubos' 1945 book and you will also find great interest in Arkwright's chapter on variation in Vol. 1 of the British "System of Bacteriology in Relation to Medicine", 1930. (Though here, page 339, he refers to phage as producing variation!) At page 319 he also gives the argument that one should not refer to "mutation" in bacteria in the absence of evidence for chromosomes. So, yes, although this is probably one of the clearer expressions of his time there is certainly some muddle!

Your questions 6-9 I will respond to more later.

On 10, Harriet Zuckerman has discussed the "marginality" of my status as a medical student but I think that I had great advantage by being geographically very close to the center, able to be deeply influenced by contacts from Avery and Demerec and Luria and Delbruck

and Ryan and Dobzhansky and yet situated as a medical student who could do research as a fling and follow my own bent. Had I been a graduate student of Dobzhansky's I don't think I would have had that freedom of action. Had I been far away from the center of action, I would not have had the very exciting stimuli and convergence of discipline. And I think you could make a similar case for Jim Watson's environment.

Before we discuss this further I would be interested to get your list of the big breakthroughs. Perhaps Francois Jacob also fits that ex-centric model.

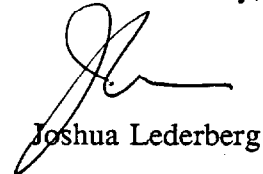
Yes, Max Zelle himself told me that he was in the competition. But I am fairly sure that Beadle had his own favorites: perhaps that might have included Adrian Srb or Gus Doermann. One will have to check the timing.

About Pasteur and anthrax I was in no way suggesting that Pasteur had plasmid loss in mind; just that the phenomenon of anthrax attenuation after a long latent period has borne some very interesting fruit.

Thank you for sending me the Bill Hayes stuff. I will respond further.

I am sure that you will deal sensitively with the discussion on Tatum's vs. my authorship of our papers. I don't know that there is much to be gained about putting that into any formal history but I thought I'd answer your curiosity.

Yours sincerely,



Joshua Lederberg

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Ryan ms 10/4/66